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(54) **PHOSPHOINOSITIDE 3-KINASE INHIBITORS**

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(56) References cited:

**WO-A1-02/02551 WO-A1-2006/127587
WO-A2-2007/084667 WO-A2-2008/094992
WO-A2-2008/145688**

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- **MOHAMMAD SAIFUDDIN ET AL:**
"Water-Accelerated Cationic [pi]-(7-endo)
Cyclisation: Application to Indole-Based
Peri-Annulated Polyheterocycles", EUROPEAN
JOURNAL OF ORGANIC CHEMISTRY, vol. 2010,
no. 26, 1 September 2010 (2010-09-01), pages
5108-5117, XP055059146, ISSN: 1434-193X, DOI:
10.1002/ejoc.201000596

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DescriptionField of the Invention

5 **[0001]** The present invention relates to novel compounds which act as inhibitors of the class IA phosphoinositide 3-kinase enzyme, PI3K-p110 δ , for the treatment of cancer, immune and inflammatory diseases.

Background of the Invention

10 **[0002]** The phosphoinositide 3-kinases (PI3Ks) constitute a family of lipid kinases involved in the regulation of a network of signal transduction pathways that control a range of cellular processes. PI3Ks are classified into three distinct sub-families, named class I, II, and III based upon their substrate specificities. Class IA PI3Ks possess a p110 α , p110 β , or p110 δ catalytic subunit complexed with one of three regulatory subunits, p85 α , p85 β or p55 δ . Class IA PI3Ks are activated by receptor tyrosine kinases, antigen receptors, G-protein coupled receptors (GPCRs), and cytokine receptors. The class IA PI3Ks primarily generate phosphatidylinositol-3,4,5-triphosphate (PI(3,4,5)P₃), a second messenger that activates the downstream target AKT. The consequences of biological activation of AKT include tumour cell progression, proliferation, survival and growth, and there is significant evidence suggesting that the PI3K/AKT pathway is dysregulated in many human cancers. Additionally, PI3K activity has been implicated in endocrinology, cardiovascular disease, immune disorders and inflammation. It has been established that PI3K-p110 δ plays a critical role in the recruitment and activation of immune and inflammatory cells. PI3K-p110 δ is also upregulated in a number of human tumours and plays a key role in tumour cell proliferation and survival.

20 **[0003]** Compounds which are able to modulate p110 δ activity have important therapeutic potential in cancer and immune and inflammatory disorders.

25 **[0004]** WO 2007/084667 A2 discloses compounds and pharmaceutically acceptable salts which inhibit kinase enzymes and are useful for the treatment and/or prevention of hyperproliferative diseases such as cancer. The compounds are also useful in the treatment of inflammation, allergy, asthma, disease and conditions of the immune system, disease and conditions of the nervous system, cardiovascular diseases, disease and conditions of the eye, dermatological diseases, osteoporosis, diabetes, multiple sclerosis, and infections.

30 **[0005]** WO 2008/094992 A2 discloses compounds useful as inhibitors of protein kinase. It also provides pharmaceutically acceptable compositions comprising said compounds and methods of using the compositions in the treatment of various disease, conditions, or disorders.

[0006] WO 2008/145688 A2 discloses compounds and salts thereof which are inhibitors of kinase activity, in particular IKK2 activity.

35 **[0007]** WO 2006/127587 A1 discloses compounds useful as inhibitors of protein kinases, particularly of JAK family and ROCK family kinases. It also provides pharmaceutically acceptable compositions comprising said compounds and methods of using the compositions in the treatment of various disease, conditions, or disorders.

40 **[0008]** Mohammad Saifuddin et al. "Water-accelerated cationic π -(7-endo) cyclisation application to indole-based periannulated polyheterocycles"; European Journal of Organic Chemistry; 2010, 5108-5117, discloses a method for the synthesis of indole-based polycyclic indolo-benzazepine and its derivatives. These compounds are used as protein kinase C inhibitors.

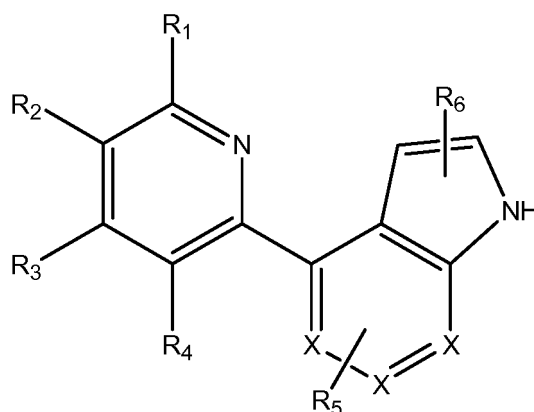
[0009] WO 02/02551 A1 discloses 4-heteroaryl-3-heteroarylidonyl-2-idolinones compounds and their physiologically acceptable salts which modulate the activity of protein kinases ("PKs"), in particular CDK2. The compounds are useful in treating disorders related to abnormal PK activity. Pharmaceutical composition containing these compounds and methods of preparing these compounds are also described.

Summary of the Invention

50 **[0010]** The present invention is a compound of formula I:

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or a pharmaceutically acceptable salt thereof,

wherein: R_1 is optionally substituted heteroaryl or heterocycle;

R_2 is C_1 - C_6 alkyl, H, halogen or $C(\text{halogen})_bR_{7(3-b)}$, where b is from 1 to 3;

R_3 is NR_7R_7 , $NR_7C(O)(C_1-C_{10}\text{alkylene})NR_8R_9$ or $NR_7C(O)(C_1-C_{10}\text{alkylene})NR_7R_7$; each R_7 is independently H or C_1 - C_6 alkyl;

R_8 and R_9 together with the nitrogen to which they are attached form a 5- to 7-membered heterocycle;

R_4 is H, halogen, optionally substituted aryl or optionally substituted alkyl;

R_5 is H;

R_6 is H;

and;

each X is independently CR_7 or N,

wherein each aryl, heteroaryl or heterocycle is optionally substituted with up to three substituents selected from C_1 - C_6 alkyl, hydroxy, C_1 - C_3 hydroxyalkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkoxy, amino, C_1 - C_3 mono alkylamino, C_1 - C_3 bis alkylamino, C_1 - C_3 acylamino, C_1 - C_3 aminoalkyl, mono (C_1 - C_3 alkyl) amino C_1 - C_3 alkyl, bis (C_1 - C_3 alkyl) amino C_1 - C_3 alkyl, C_1 - C_3 -acylamino, C_1 - C_3 alkyl sulfonylamino, halo, nitro, cyano, trifluoromethyl, carboxy, C_1 - C_3 alkoxycarbonyl, aminocarbonyl, mono C_1 - C_3 alkyl aminocarbonyl, bis C_1 - C_3 alkyl aminocarbonyl, $-SO_3H$, C_1 - C_3 alkylsulfonyl, aminosulfonyl, mono C_1 - C_3 alkyl aminosulfonyl and bis C_1 - C_3 -alkyl aminosulfonyl.

Description of Preferred Embodiments

[0011] As used herein, "alkyl" means a C_1 - C_{10} alkyl group, which can be linear or branched. Preferably, it is a C_1 - C_6 alkyl moiety. More preferably, it is a C_1 - C_4 alkyl moiety. Examples include methyl, ethyl, n-propyl and t-butyl. It may be divalent, e.g. propylene. In general, the suffix "-ene" means that the group is divalent.

[0012] As used herein, "cycloalkyl" contains from 3 to 10 carbon atoms. It may be monovalent or divalent.

[0013] As used herein, "alkenyl" means a C_2 - C_{10} alkenyl group. Preferably, it is a C_2 - C_6 alkenyl group. More preferably, it is a C_2 - C_4 alkenyl group. The alkenyl radicals may be mono- or di-saturated, more preferably monosaturated. Examples include vinyl, allyl, 1-propenyl, isopropenyl and 1-butenyl. It may be divalent, e.g. propenylene

[0014] As used herein, "alkynyl" is a C_2 - C_{10} alkynyl group which can be linear or branched. Preferably, it is a C_2 - C_4 alkynyl group or moiety. It may be divalent.

[0015] Each of the C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl and C_2 - C_{10} alkynyl groups may be optionally substituted with each other, i.e. C_1 - C_{10} alkyl optionally substituted with C_2 - C_{10} alkenyl. They may also be optionally substituted with aryl, cycloalkyl (preferably C_3 - C_{10}), aryl or heteroaryl. They may also be substituted with any of the "optional substituents" defined below.

[0016] As used herein, "aryl" means a monocyclic, bicyclic, or tricyclic monovalent or divalent aromatic radical, such as phenyl, biphenyl, naphthyl, anthracenyl, which can be optionally substituted with up to five substituents preferably selected from the group of C_1 - C_6 alkyl, hydroxy, C_1 - C_3 hydroxyalkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkoxy, amino, C_1 - C_3 mono alkylamino, C_1 - C_3 bis alkylamino, C_1 - C_3 acylamino, C_1 - C_3 aminoalkyl, mono (C_1 - C_3 alkyl) amino C_1 - C_3 alkyl, bis(C_1 - C_3 alkyl) amino C_1 - C_3 alkyl, C_1 - C_3 -acylamino, C_1 - C_3 alkyl sulfonylamino, halo, nitro, cyano, trifluoromethyl, carboxy, C_1 - C_3 alkoxycarbonyl, aminocarbonyl, mono C_1 - C_3 alkyl aminocarbonyl, bis C_1 - C_3 alkyl aminocarbonyl, $-SO_3H$, C_1 - C_3 alkylsulfonyl, aminosulfonyl, mono C_1 - C_3 alkyl aminosulfonyl and bis C_1 - C_3 -alkyl aminosulfonyl.

[0017] As used herein, "heteroaryl" means a monocyclic, bicyclic or tricyclic monovalent aromatic radical containing up to four heteroatoms selected from oxygen, nitrogen and sulfur, such as thiazolyl, tetrazolyl, imidazolyl, oxazolyl,

isoxazolyl, thienyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, said radical being optionally substituted with up to three substituents preferably selected from the group of C₁-C₆ alkyl, hydroxy, C₁-C₃ hydroxyalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, amino, C₁-C₃ mono alkylamino, C₁-C₃ bis alkylamino, C₁-C₃ acylamino, C₁-C₃ aminoalkyl, mono (C₁-C₃ alkyl) amino C₁-C₃ alkyl, bis (C₁-C₃ alkyl) amino C₁-C₃ alkyl, C₁-C₃-acylamino, C₁-C₃ alkyl sulfonylamino, halo, nitro, cyano, trifluoromethyl, carboxy, C₁-C₃ alkoxycarbonyl, aminocarbonyl, mono C₁-C₃ alkyl aminocarbonyl, bis C₁-C₃ alkyl aminocarbonyl, -SO₃H, C₁-C₃ alkylsulfonyl, aminosulfonyl, mono C₁-C₃ alkyl aminosulfonyl and bis C₁-C₃-alkyl aminosulfonyl.

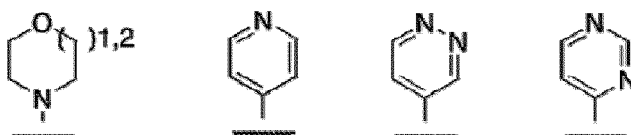
[0018] As used herein, "heterocycle" is a mono- or di-valent non-aromatic carbocyclic radical containing up to 4 heteroatoms selected from oxygen, nitrogen and sulfur. The word 'linker' has been used herein to mean di-valent. If the heterocycle is a di-valent linker, the heterocycle may be attached to neighbouring groups through a carbon atom, or through one of the heteroatoms, e.g. a N.

[0019] The above groups can be followed by the suffix -ene. This means that the group is divalent, i.e. a linker group.

[0020] As used herein, "optionally substituted" preferably means optionally substituted with up to three "optional substituents" selected from C₁-C₆ alkyl, hydroxy, C₁-C₃ hydroxyalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, amino, C₁-C₃ mono alkylamino, C₁-C₃ bis alkylamino, C₁-C₃ acylamino, C₁-C₃ aminoalkyl, mono (C₁-C₃ alkyl) amino C₁-C₃ alkyl, bis (C₁-C₃ alkyl) amino C₁-C₃ alkyl, C₁-C₃-acylamino, C₁-C₃ alkyl sulfonylamino, halo e.g. F, Cl, nitro, cyano, trifluoromethyl, carboxy, C₁-C₃ alkoxycarbonyl, aminocarbonyl, mono C₁-C₃ alkyl aminocarbonyl, bis C₁-C₃ alkyl aminocarbonyl, -SO₃H, C₁-C₃ alkylsulfonyl, aminosulfonyl, mono C₁-C₃ alkyl aminosulfonyl and bis C₁-C₃-alkyl aminosulfonyl.

[0021] In R₄, preferably halogen is fluorine.

[0022] R₁ is an optionally substituted aryl or optionally substituted heterocycle, preferably a nitrogen-containing one. More preferably, R₁ is morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, cyclohexylamino, cyclopentylamino, piperidin-4-yl, N-acetylpiperazinyl, thiomorpholinyl, thiomorpholinyldioxide, 4-hydroxyethylpiperidinyl, and 4-hydroxypiperidinyl. Still more preferably, R₁ is represented by any of the following structures:



[0023] Most preferably, R₁ is morpholino.

[0024] R₂ is C₁-C₆ alkyl, H, halogen or C(halogen)_bR_{7(3-b)}, where b is from 1 to 3. More preferably R₂ is C₁-C₆ alkyl or H. More preferably R₂ is H.

[0025] In a preferred embodiment at least one X is CH. Preferably, each X is CH.

[0026] Preferably, R₂ is H.

[0027] Preferably, R₄ is H.

[0028] R₅ and R₆ are H.

[0029] Preferably, R₃ is NR₇R₇.

[0030] Preferably, R₃ is NR₇C(O)(C₁-C₁₀ alkylene)NR₈R₉.

[0031] Preferably, R₃ is NR₇C(O)(C₁-C₁₀ alkylene)NR₇R₇.

[0032] In a preferred embodiment, a compound of the invention is as exemplified herein, i.e. compound A, B or C.

[0033] For the avoidance of doubt, a moiety designated as, for example, -C(O)NR₇-, is not direction specific, it can also be positioned as -NR₇-C(O)-.

[0034] A pharmaceutical composition of the invention typically contains up to 85 wt% of a compound of the invention. More typically, it contains up to 50 wt% of a compound of the invention. Preferred pharmaceutical compositions are sterile and pyrogen-free. Further, the pharmaceutical compositions provided by the invention typically contain a compound of the invention which is a substantially pure optical isomer. Preferably, the pharmaceutical composition comprises a pharmaceutically acceptable salt form of a compound of the invention.

[0035] As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulfonic, ethanesulfonic, salicylic, stearic, benzenesulfonic or *p*-toluenesulfonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, aryl amines or heterocyclic amines.

[0036] For the avoidance of doubt, the present invention also discloses prodrugs which react *in vivo* to give a compound of the present invention.

[0037] The compounds of the invention may be prepared by synthetic routes that will be apparent to those skilled in the art, e.g. based on the Examples.

[0038] The compounds of the invention and compositions comprising them may be administered in a variety of dosage forms. In one embodiment, a pharmaceutical composition comprising a compound of the invention may be formulated in a format suitable for oral, rectal, parenteral, intranasal or transdermal administration or administration by inhalation or by suppository. Typical routes of administration are parenteral, intranasal or transdermal administration or administration by inhalation.

[0039] The compounds of the invention can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. Preferred pharmaceutical compositions of the invention are compositions suitable for oral administration, for example tablets and capsules.

[0040] The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

[0041] The compounds of the invention may also be administered by inhalation. An advantage of inhaled medications is their direct delivery to the area of rich blood supply in comparison to many medications taken by oral route. Thus, the absorption is very rapid as the alveoli have an enormous surface area and rich blood supply and first pass metabolism is bypassed. A further advantage may be to treat diseases of the pulmonary system, such that delivering drugs by inhalation delivers them to the proximity of the cells which are required to be treated.

[0042] The present invention also provides an inhalation device containing such a pharmaceutical composition. Typically said device is a metered dose inhaler (MDI), which contains a pharmaceutically acceptable chemical propellant to push the medication out of the inhaler.

[0043] The compounds of the invention may also be administered by intranasal administration. The nasal cavity's highly permeable tissue is very receptive to medication and absorbs it quickly and efficiently, more so than drugs in tablet form. Nasal drug delivery is less painful and invasive than injections, generating less anxiety among patients. By this method absorption is very rapid and first pass metabolism is usually bypassed, thus reducing inter-patient variability. Further, the present invention also provides an intranasal device containing such a pharmaceutical composition.

[0044] The compounds of the invention may also be administered by transdermal administration. The present invention therefore also provides a transdermal patch containing a compound of the invention.

[0045] The compounds of the invention may also be administered by sublingual administration. The present invention therefore also provides a sub-lingual tablet comprising a compound of the invention.

[0046] A compound of the invention may also be formulated with an agent which reduces degradation of the substance by processes other than the normal metabolism of the patient, such as anti-bacterial agents, or inhibitors of protease enzymes which might be the present in the patient or in commensural or parasite organisms living on or within the patient, and which are capable of degrading the compound.

[0047] Liquid dispersions for oral administration may be syrups, emulsions and suspensions.

[0048] Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

[0049] Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

[0050] The compounds of the present invention can be used in both the treatment and prevention of cancer and can be used in a monotherapy or in a combination therapy. When used in a combination therapy, the compounds of the present invention are typically used together with small chemical compounds such as platinum complexes, anti-metabolites, DNA topoisomerase inhibitors, radiation, antibody-based therapies (for example herceptin and rituximab), anti-cancer vaccination, gene therapy, cellular therapies, hormone therapies or cytokine therapy.

[0051] In one embodiment of the invention a compound of the invention is used in combination with another chemotherapeutic or antineoplastic agent in the treatment of a cancer. Examples of such other chemotherapeutic or antineoplastic agents include platinum complexes including cisplatin and carboplatin, mitoxantrone, vinca alkaloids for example vincristine and vinblastine, anthracycline antibiotics for example daunorubicin and doxorubicin, alkylating agents for example chlorambucil and melphalan, taxanes for example paclitaxel, antifolates for example methotrexate and tomudex, epipodophyllotoxins for example etoposide, camptothecins for example irinotecan and its active metabolite SN38 and DNA methylation inhibitors for example the DNA methylation inhibitors disclosed in WO02/085400.

[0052] According to the invention, therefore, products are provided which contain a compound of the invention and another chemotherapeutic or antineoplastic agent as a combined preparation for simultaneous, separate or sequential use in alleviating a cancer. Also provided according to the invention is the use of compound of the invention in the manufacture of a medicament for use in the alleviation of cancer by co-administration with another chemotherapeutic or antineoplastic agent. The compound of the invention and the said other agent may be administered in any order. In both these cases the compound of the invention and the other agent may be administered together or, if separately, in any order as determined by a physician.

[0053] The PI3K inhibitors of the present invention may also be used to treat abnormal cell proliferation due to insults to body tissue during surgery. These insults may arise as a result of a variety of surgical procedures such as joint surgery, bowel surgery, and cheloid scarring. Diseases that produce fibrotic tissue that may be treated using the PI3K inhibitors of the present invention include emphysema. Repetitive motion disorders that may be treated using the present invention include carpal tunnel syndrome. An example of a cell proliferative disorder that may be treated using the invention is a bone tumour.

[0054] Proliferative responses associated with organ transplantation that may be treated using PI3K inhibitors of the invention include proliferative responses contributing to potential organ rejections or associated complications. Specifically, these proliferative responses may occur during transplantation of the heart, lung, liver, kidney, and other body organs or organ systems.

[0055] Abnormal angiogenesis that may be treated using this invention include those abnormal angiogenesis accompanying rheumatoid arthritis, ischemic-reperfusion related brain edema and injury, cortical ischemia, ovarian hyperplasia and hypervascularity, polycystic ovary syndrome, endometriosis, psoriasis, diabetic retinopathy, and other ocular angiogenic diseases such as retinopathy of prematurity (retrolental fibroplastic), macular degeneration, corneal graft rejection, neurovascular glaucoma and Oster Webber syndrome.

[0056] Examples of diseases associated with uncontrolled angiogenesis that may be treated according to the present invention include, but are not limited to retinal/choroidal neovascularisation and corneal neovascularisation. Examples of diseases which include some component of retinal/choroidal neovascularisation include, but are not limited to, Best's diseases, myopia, optic pits, Stargart's diseases, Paget's disease, vein occlusion, artery occlusion, sickle cell anaemia, sarcoid, syphilis, pseudoxanthoma elasticum carotid apo structuve diseases, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosus, retinopathy of prematurity, Eale's disease, diabetic retinopathy, macular degeneration, Bechet's diseases, infections causing a retinitis or chroiditis, presumed ocular histoplasmosis, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications, diseases associated with rubesis (neovascularisation of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy. Examples of corneal neovascularisation include, but are not limited to, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phlyectenulosis, diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, polyarteritis, Wegener sarcoidosis, Scleritis, periphigoid radial keratotomy, neovascular glaucoma and retrolental fibroplasia, syphilis, Mycobacteria infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, Herpes simplex infections, Herpes zoster infections, protozoan infections and Kaposi sarcoma.

[0057] Chronic inflammatory diseases associated with uncontrolled angiogenesis may also be treated using PI3K inhibitors of the present invention. Chronic inflammation depends on continuous formation of capillary sprouts to maintain an influx of inflammatory cells. The influx and presence of the inflammatory cells produce granulomas and thus maintains the chronic inflammatory state. Inhibition of angiogenesis using a PI3K inhibitor alone or in conjunction with other anti-inflammatory agents may prevent the formation of the granulomas and thus alleviate the disease. Examples of chronic inflammatory diseases include, but are not limited to, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, psoriasis, sarcoidosis, and rheumatoid arthritis.

[0058] Inflammatory bowel diseases such as Crohn's disease and ulcerative colitis are characterised by chronic inflammation and angiogenesis at various sites in the gastrointestinal tract. For example, Crohn's disease occurs as a chronic transmural inflammatory disease that most commonly affects the distal ileum and colon but may also occur in any part of the gastrointestinal tract from the mouth to the anus and perianal area. Patients with Crohn's disease generally have chronic diarrhoea associated with abdominal pain, fever, anorexia, weight loss and abdominal swelling. Ulcerative colitis is also a chronic, nonspecific, inflammatory and ulcerative disease arising in the colonic mucosa and is characterised by the presence of bloody diarrhoea. These inflammatory bowel diseases are generally caused by chronic granulomatous inflammation throughout the gastrointestinal tract, involving new capillary sprouts surrounded by a cylinder of inflammatory cells. Inhibition of angiogenesis by these inhibitors should inhibit the formation of the sprouts and prevent the formation of granulomas. Inflammatory bowel diseases also exhibit extra intestinal manifestations, such as skin lesions. Such lesions are characterized by inflammation and angiogenesis and can occur at many sites other than the gastrointestinal tract. Inhibition of angiogenesis by PI3K inhibitors according to the present invention can reduce the influx of inflammatory cells and prevent lesion formation.

[0059] Sarcoidosis, another chronic inflammatory disease, is characterized as a multisystem granulomatous disorder. The granulomas of this disease can form anywhere in the body. Thus, the symptoms depend on the site of the granulomas and whether the disease is active. The granulomas are created by the angiogenic capillary sprouts providing a constant supply of inflammatory cells. By using PI3K inhibitors according to the present invention to inhibit angiogenesis, such granulomas formation can be inhibited. Psoriasis, also a chronic and recurrent inflammatory disease, is characterised by papules and plaques of various sizes. Treatment using these inhibitors alone or in conjunction with other anti-inflammatory agents should prevent the formation of new blood vessels necessary to maintain the characteristic lesions and

provide the patient relief from the symptoms.

[0060] Rheumatoid arthritis (RA) is also a chronic inflammatory disease characterised by non-specific inflammation of the peripheral joints. It is believed that the blood vessels in the synovial lining of the joints undergo angiogenesis. In addition to forming new vascular networks, the endothelial cells release factors and reactive oxygen species that lead to pannus growth and cartilage destruction. The factors involved in angiogenesis may actively contribute to, and help maintain, the chronically inflamed state of rheumatoid arthritis. Treatment using PI3K inhibitors according to the present invention alone or in conjunction with other anti-RA agents may prevent the formation of new blood vessels necessary to maintain the chronic inflammation.

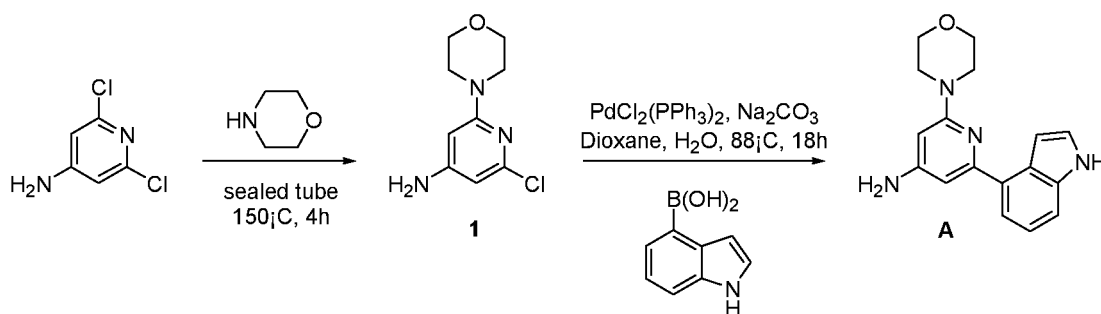
[0061] Preferably, the condition is cancer, notably leukaemias including chronic myelogenous leukaemia and acute myeloid leukaemia, lymphomas, solid tumours, and PTEN-negative tumours including PTEN-negative haematological, breast, lung, endometrial, skin, brain and prostate cancers (where PTEN refers to "phosphatase and tensin homolog deleted on chromosome 10"). More preferably, the condition to be treated by a compound of the invention is rheumatoid arthritis, asthma, chronic obstructive pulmonary disease (COPD), multiple sclerosis, psoriasis and other inflammatory skin disorders, systemic lupus erythematosus, inflammatory bowel disease, and organ transplant rejection. More preferably,

[0062] The invention will now be illustrated by the following Examples.

Examples

A. 2-(1H-Indol-4-yl)-6-morpholin-4-yl-pyridin-4-ylamine, 2

[0063]



i) Synthesis of 2-chloro-6-morpholin-4-ylpyridin-4-ylamine, 1

[0064] A sealed tube charged with 2,6-dichloro-pyridin-4-ylamine (500mg, 3.1 mmol, 1eq) and morpholine (2.3mL, 26.3mmol, 9eq) was heated up to 150°C for 4h. Once cooled down, the reaction mixture was partitioned with H₂O (10mL) and extracted with EtOAc (3 x 20mL). The combined organic extracts were washed with H₂O (2 x 5mL), dried over MgSO₄, and the solvent was removed *in vacuo*. The resulting residue was further purified by silica gel column chromatography with hexane/EtOAc (1:1-2:3) to furnish 1 as a pink solid (555mg, 85%).

¹H NMR (400MHz, DMSO-*d*₆) δ_H ppm: 6.03 (s, 2H), 5.95 (d, *J*=1.4Hz, 1H), 5.75 (d, *J*=1.4Hz, 1H), 3.62-3.67 (m, 4H), 3.23-3.28 (m, 4H); MS (ES⁺) 214.1 (100%, [M+H]⁺).

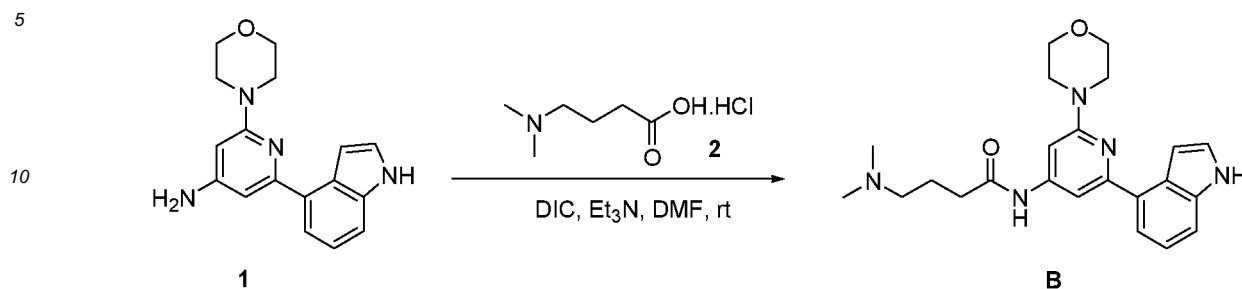
ii) Synthesis of 2-(1H-indol-4-yl)-6-morpholin-4-ylpyridin-4-ylamine, A

[0065] To a flask charged with indole-4-boronic acid (791mg, 4.91mmol, 3eq), dichloro-bis(triphenylphosphine)palladium (II) (230mg, 0.33mmol, 0.2eq) and sodium carbonate (348mg, 3.28mmol, 2eq), was added compound 1 (350mg, 1.64mmol, 1eq) dissolved in dioxane/water (40mL, 3:1). The resulting reaction mixture was then heated at 88°C for 18h under Ar(g); once cooled down, it was then partitioned with H₂O (20mL) and extracted with EtOAc (4 x 20mL) and CH₂Cl₂ (15mL). The combined organic extracts were dried over MgSO₄ and the solvent was then removed *in vacuo*. The residue was further purified by silica gel column chromatography, eluting with hexane/EtOAc (1:1-0:1), to yield the product as a white solid (273mg, 56%).

¹H NMR (400MHz, DMSO-*d*₆) δ_H ppm: 11.12 (br. s., 1H), 7.39 (s, 1H), 7.35-7.38 (m, 2H), 7.12 (s, 1H), 6.87 (br. s., 1H), 6.56 (s, 1H), 5.85-5.88 (m, 1H), 5.74 (br. s., 2H), 3.68-3.74 (m, 4H), 3.37-3.42 (m, 4H); MS (ES⁺) 295.0 (100%, [M+H]⁺).

B. 4-Dimethylamino-N-[2-(1H-indol-4-yl)-6-morpholin-4-yl-pyridin-4-yl]-butyramide

[0066]

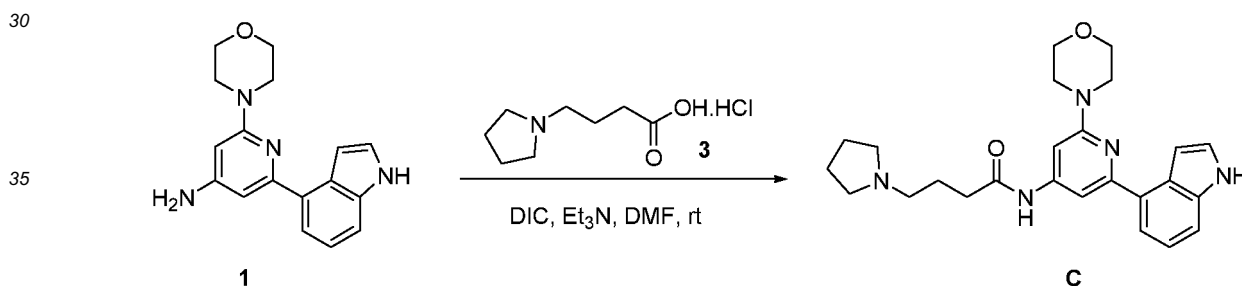


15 [0067] To a solution of 4-dimethylamino-butyric acid hydrochloride, 2 (29mg, 0.17mmol, 2eq) and DIC (26μL, 0.17mmol, 2eq) in DMF (1mL) was added Et₃N (48mL, 0.34mmol, 4eq) at rt. After 30 min, amine 1 (25mg, 0.085mmol, 1eq) was dissolved in DMF (1mL) and was added to the reaction mixture, which was then heated at 60°C for 4h. Once cooled down, the reaction mixture was partitioned with NaHCO₃ (10mL) and extracted with EtOAc (3 x 10mL). The combined organic extracts were dried over MgSO₄ and the solvent was removed *in vacuo*. The resulting residue was further purified by silica gel column chromatography with CH₂Cl₂/MeOH (1:0-9:1+0.3M NH₃) to furnish the product as a white solid (26mg, 74%).

20 ¹H NMR (400MHz, CDCl₃) δ_H ppm: 10.44 (br. s, 1H), 8.28 (br. s, 1H), 7.54 (d, J=7.4Hz, 1H), 7.43 (d, J=8.1Hz, 1H), 7.37 (s, 1H), 7.24-7.30 (m, 2H), 7.07-7.10 (m, 1H), 7.00 (d, J=0.9Hz, 1H), 3.83-3.88 (m, 4H), 3.63-3.68 (m, 4H), 2.53-2.59 (m, 2H), 2.51 (t, J=5.9Hz, 2H), 2.36 (s, 6H), 1.90 (quin, J=6.1Hz, 2H); MS (ES⁺) 408.0 (100%, [M+H]⁺).

C. N-[2-(1H-Indol-4-yl)-6-morpholin-4-yl-pyridin-4-yl]-4-pyrrolidin-1-yl-butyramide

[0068]



40 [0069] To a solution of 4-pyrrolidin-1-yl-butyric acid hydrochloride, 3, (33mg, 0.17mmol, 2eq) and DIC (26μL, 0.17mmol, 2eq) in DMF (1mL) was added Et₃N (47mL, 0.34mmol, 4eq) at rt. After 30 min, the amine 1 (25mg, 0.085mmol, 1eq) was dissolved in DMF (1mL) and was added to the reaction mixture, which was then heated at 60°C for 4h. Once cooled, the reaction mixture was partitioned with NaHCO₃ (10mL) and extracted with EtOAc (3 x 10mL) and CH₂Cl₂ (10mL). The combined organic extracts were dried over MgSO₄ and the solvent was removed *in vacuo*. The resulting residue was further purified by silica gel column chromatography, eluting with CH₂Cl₂:MeOH (1:0-6:1+0.3M NH₃) to furnish the product as a white solid (4.5mg, 12%).

45 ¹H NMR (400MHz, CDCl₃) δ_H ppm: 7.48 (d, J=7.3Hz, 1H), 7.41 (d, J=8.1Hz, 1H), 7.32 (s, 1H), 7.25 (m, J=3.0Hz, 1H), 7.18 (t, J=7.7Hz, 1H), 7.12 (s, 1H), 6.95-6.98 (m, 1H), 3.79-3.85 (m, 4H), 3.58 (t, J=4.6Hz, 4H), 3.26-3.36 (m, 2H), 3.08-3.13 (m, 1H), 3.01 (t, J=7.5Hz, 2H), 2.54 (t, J=7.0Hz, 2H), 2.46 (t, J=6.7Hz, 1H), 1.93-2.08 (m, 4H), 1.16 (t, J=7.1Hz, 1H), 1.08 (t, J=7.2Hz, 1H); MS (ES⁺) 434.0 (100%, [M+H]⁺).

50 [0070] The following biochemical data have been generated for the exemplified compounds, showing PI3K binding potency.

Biochemical Data

55

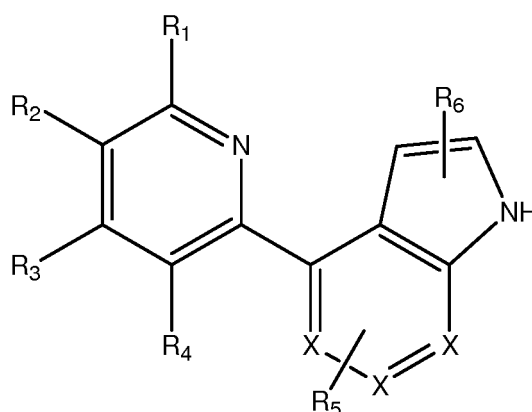
Compound	IC ₅₀ (nM), PI3K-p110α	IC ₅₀ (nM), PI3K-p110β	IC ₅₀ (nM), PI3K-p110δ	IC ₅₀ (nM), PI3K-p110γ
B	≥ 10,000	247	177	≥ 10,000

(continued)

Compound	IC ₅₀ (nM), PI3K-p110 α	IC ₅₀ (nM), PI3K-p110 β	IC ₅₀ (nM), PI3K-p110 δ	IC ₅₀ (nM), PI3K-p110 γ
C			953	

Claims

1. A compound of formula I:



or a pharmaceutically acceptable salt thereof,
wherein:

R₁ is optionally substituted heteroaryl or heterocycle;

R₂ is C₁-C₆ alkyl, H, halogen or C(halogen)_bR_{7(3-b)}, where b is from 1 to 3;

R₃ is NR₇R₇, NR₇C(O)(C₁-C₁₀alkylene)NR₈R₉ or NR₇C(O)(C₁-C₁₀ alkylene)NR₇R₇;
each R₇ is independently H or C₁-C₆ alkyl;

R₈ and R₉ together with the nitrogen to which they are attached form a 5- to 7-membered heterocycle;

R₄ is H, halogen, optionally substituted aryl or optionally substituted alkyl;

R₅ is H;

R₆ is H;

and each X is independently CR₇ or N,

wherein each aryl, heteroaryl or heterocycle is optionally substituted with up to three substituents selected from C₁-C₆ alkyl, hydroxy, C₁-C₃ hydroxyalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, amino, C₁-C₃ mono alkylamino, C₁-C₃ bis alkylamino, C₁-C₃ acylamino, C₁-C₃ aminoalkyl, mono (C₁-C₃ alkyl) amino C₁-C₃ alkyl, bis (C₁-C₃ alkyl) amino C₁-C₃ alkyl, C₁-C₃-acylamino, C₁-C₃ alkyl sulfonylamino, halo, nitro, cyano, trifluoromethyl, carboxy, C₁-C₃ alkoxy carbonyl, aminocarbonyl, mono C₁-C₃ alkyl aminocarbonyl, bis C₁-C₃ alkyl aminocarbonyl, -SO₃H, C₁-C₃ alkylsulfonyl, aminosulfonyl, mono C₁-C₃ alkyl aminosulfonyl and bis C₁-C₃-alkyl aminosulfonyl.

2. A compound according to claim 1, wherein R₁ is morpholino and/or wherein R₂ is H and/or wherein R₄ is H.

3. A compound according to any preceding claim, wherein each X is CH.

4. A compound according to any preceding claim, which is selected from:

2-(1H-indol-4-yl)-6-morpholin-4-yl-pyridin-4-ylamine;

4-dimethylamino-N-[2-(1H-indol-4-yl)-6-morpholin-4-yl-pyridin-4-yl]-butyramide; and

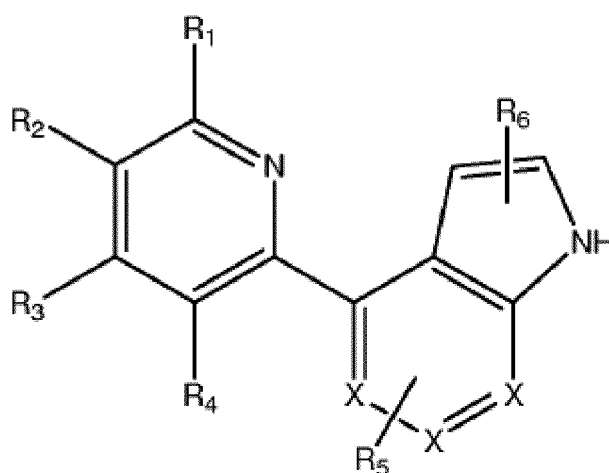
N-[2-(1H-indol-4-yl)-6-morpholin-4-yl-pyridin-4-yl]-4-pyrrolidin-1-yl-butylamide.

5. A pharmaceutical composition comprising a compound according to any preceding claim, and a pharmaceutically acceptable excipient.

6. A compound or composition according to any preceding claim, for use in therapy.
7. A compound or composition for use according to claim 6, wherein the therapy is of cancer, an immune disorder or an inflammatory disorder.
8. A compound or composition for use according to claim 7, wherein the cancer is a leukaemia or a PTEN-negative solid tumour.
9. A compound for use according to claim 6 or claim 7, wherein the therapy is of rheumatoid arthritis.
10. A compound or composition for use according to claim 6, for use in antirejection therapy following an organ transplant.

Patentansprüche

1. Verbindung mit der Formel I:



oder ein pharmazeutisch unbedenkliches Salz davon,
wobei:

R_1 optional substituiertes Heteroaryl oder Heterocyclus ist;
 R_2 optional C_1 - C_6 -Alkyl, H, Halogen oder $C(\text{halogen})_b R_{7(3-b)}$ wobei b von 1 bis 3 ist;
 R_3 NR_7R_7 , $NR_7C(O)(C_1-C_{10}\text{-Alkyl})NR_8R_9$ oder $NR_7C(O)(C_1-C_{10}\text{-Alkyl})NR_7R_7$ ist;
 jedes R_7 unabhängig H oder C_1 - C_6 -Alkyl ist;
 R_8 und R_9 zusammen mit dem Stickstoff, an den sie gebunden sind, einen 5- bis 7-gliedrigen Heterocyclus ausbilden;
 R_4 H, Halogen, optional substituiertes Aryl oder optional substituiertes Alkyl ist;
 R_5 H ist;
 R_6 H ist;
 und jedes X unabhängig CR_7 oder N ist,
 wobei jedes Aryl, Heteroaryl oder Heterocyclus optional mit bis zu drei Substituenten substituiert ist, ausgewählt aus C_1 - C_6 -Alkyl, Hydroxy, C_1 - C_3 -Hydroxyalkyl, C_1 - C_3 -Alkoxy, C_1 - C_3 -Haloalkoxy, Amino, C_1 - C_3 -Monoalkylamino, C_1 - C_3 -Bisalkylamino, C_1 - C_3 -Acylamino, C_1 - C_3 -Aminoalkyl, Mono(C_1 - C_3 -alkyl)amino- C_1 - C_3 -alkyl, Bis(C_1 - C_3 -alkyl)amino- C_1 - C_3 -alkyl, C_1 - C_3 -Acylamino, C_1 - C_3 -Alkylsulfonylamino, Halo, Nitro, Cyano, Trifluoromethyl, Carboxy, C_1 - C_3 -Alkoxy-carbonyl, Aminocarbonyl, Mono- C_1 - C_3 -alkylaminocarbonyl, Bis- C_1 - C_3 -alkylaminocarbonyl, $-SO_3H$, C_1 - C_3 -Alkylsulfonyl, Aminosulfonyl, Mono- C_1 - C_3 -alkylaminosulfonyl und Bis- C_1 - C_3 -alkylaminosulfonyl.

2. Verbindung nach Anspruch 1, wobei R_1 Morpholino ist und/oder wobei R_2 H ist und/oder wobei R_4 H ist.
3. Verbindung nach einem der vorhergehenden Ansprüche, wobei jedes X CH ist.

4. Verbindung nach einem der vorhergehenden Ansprüche, die ausgewählt ist aus:

2-(1H-indol-4-yl)-6-morpholin-4-ylpyridin-4-ylamin; 4-Dimethylamino-N-[2-(1H-indol-4-yl)-6-morpholin-4-ylpyridin-4-yl]-butyramid;
und
N-[2-(1H-indol-4-yl)-6-morpholin-4-ylpyridin-4-yl]-4-pyrrolidin-1-ylbutyramid.

5. Pharmazeutische Zusammensetzung, eine Verbindung nach einem der vorhergehenden Ansprüche und einen pharmazeutisch unbedenklichen Arzneistoffträger umfassend.

6. Verbindung oder Zusammensetzung nach einem der vorhergehenden Ansprüche zur Verwendung in Therapie.

7. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 6, wobei die Therapie für Krebs, eine Immunerkrankung oder eine Entzündungskrankheit ist.

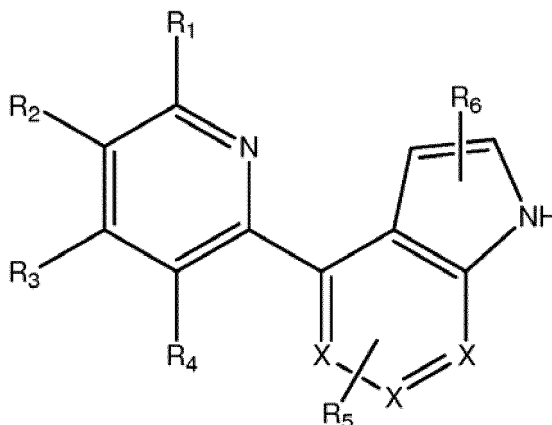
8. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 7, wobei der Krebs Leukämie oder ein PTEN-negativer fester Tumor ist.

9. Verbindung oder Zusammensetzung nach Anspruch 6 oder 7, wobei die Therapie für rheumatoider Arthritis ist.

10. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 6 zur Verwendung in einer Anti-Abstoßungs-Therapie nach einer Organtransplantation.

Revendications

1. Composé de la formule I :



ou un sel pharmaceutiquement acceptable de celui-ci,
où :

R₁ représente éventuellement un hétéroaryle ou un hétérocycle substitué ;

R₂ représente un alkyle en C₁-C₆, H, un halogène ou un C(halogène)_bR_{7(3-b)}, où b est compris entre 1 et 3 ;

R₃ représente NR₇R₇, NR₇C(O)(alkylène en C₁-C₁₀)NR₈R₉ ou NR₇C(O)(alkylène en C₁-C₁₀)NR₇R₇ ;

chaque R₇ représente indépendamment H ou un alkyle en C₁-C₆ ;

R₈ et R₉, conjointement avec l'azote auquel ils sont liés, forment un hétérocycle de 5 à 7 chaînons ;

R₄ représente H, un halogène, un aryle éventuellement substitué ou un alkyle éventuellement substitué ;

R₅ représente H ;

R₆ représente H ;

et chaque X représente indépendamment CR₇ ou N,

chaque aryle, hétéroaryle ou hétérocycle étant éventuellement substitué par trois substituants maximum choisis parmi alkyle en C₁-C₆, hydroxy, hydroxyalkyle en C₁-C₃, alcoxy en C₁-C₃, haloalcoxy en C₁-C₃, amino, monoalkylamino en C₁-C₃, bis-alkylamino en C₁-C₃, acylamino en C₁-C₃, aminoalkyle en C₁-C₃, mono(alkyle en

C₁-C₃)-aminoalkyle en C₁-C₃, bis(alkyle en C₁-C₃)-aminoalkyle en C₁-C₃, acylamino en C₁-C₃, alkylsulfonyl-
amino en C₁-C₃, halo, nitro, cyano, trifluorométhyle, carboxy, alcoxycarbonyl en C₁-C₃, aminocarbonyl, mono-
alkylaminocarbonyl en C₁-C₃, bis-alkylaminocarbonyl en C₁-C₃, -SO₃H, alkylsulfonyl en C₁-C₃, aminosul-
fonyl, mono-alkylaminosulfonyl en C₁-C₃ et bis-alkylaminosulfonyl en C₁-C₃.

2. Composé selon la revendication 1, dans lequel R₁ représente morpholino et/ou dans lequel R₂ représente H et/ou dans lequel R₄ représente H.
3. Composé selon l'une quelconque des revendications précédentes, dans lequel chaque X représente CH.
4. Composé selon l'une quelconque des revendications précédentes, qui est choisi parmi :
2-(1H-indol-4-yl)-6-morpholin-4-yl-pyridin-4-ylamine ; 4-diméthylamino-N-[2-(1H-indol-4-yl)-6-morpholin-4-yl-
pyridin-4-yl]-butyramide ; et
N-[2-(1H-indol-4-yl)-6-morpholin-4-yl-pyridin-4-yl]-4-pyrrolidin-1-yl-butylamide.
5. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications précédentes et un excipient pharmaceutiquement acceptable.
6. Composé ou composition selon l'une quelconque des revendications précédentes, à utiliser en thérapie.
7. Composé ou composition à utiliser selon la revendication 6, dans lequel la thérapie est celle contre le cancer, un trouble immunitaire ou un trouble inflammatoire.
8. Composé ou composition à utiliser selon la revendication 7, dans lequel le cancer est une leucémie ou une tumeur solide négative au PTEN.
9. Composé à utiliser selon la revendication 6 ou la revendication 7, dans lequel la thérapie est celle contre la polyarthrite rhumatoïde.
10. Composé ou composition à utiliser selon la revendication 6, à utiliser dans la thérapie anti-rejet suite à une greffe d'organe.

REFERENCES CITED IN THE DESCRIPTION

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